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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03251047.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Composition

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
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J7171 (V) FF

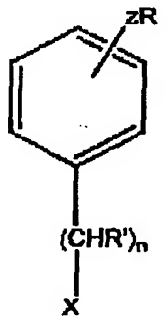
COMPOSITION

The present invention relates to an oral composition comprising a salt of an alkyl hydroxybenzoate.

Salts of alkyl hydroxybenzoates (parabens) are known in the art where the alkyl group is methyl, ethyl, propyl or butyl in The Handbook of Pharmaceutical Excipients, A.H Kibbe ed, Pharmaceutical Press, London.

We have found that there exists a range of compounds which exhibit surprisingly high antibacterial efficacy and are not disclosed for use in oral compositions in the prior art.

Accordingly, the invention provides an oral composition comprising a compound of Formula 1:



Formula (1),

wherein:

at least one R is an alkali metal salt of -OH, the remaining R groups independently selected from the group consisting

of: H, F, Cl, Br, -OH, C_1 to C_5-alkyl, -C(O)H, and -C(O)-C_1 to C_5-alkyl and z is from 1 to 5;

R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', and $-SO_2$-R'' and R'' is selected from the group consisting of: $-C_5$-$_{12}$ alkyl or $-CH_2C_6H_6$.

In a preferred embodiment X is-C(O)O-R'', wherein R'' is a substituted or unsubstituted branched or straight chain hydrocarbon moiety comprising from 5 to 16 and especially from 7 to 10 carbon atoms. Examples of suitable R'' groups include pentyl, hexyl, benzyl, heptyl, octyl, 2-ethyl hexyl, nonyl, decyl, undecyl, dodecyl and tridecyl. Of these the most preferred are the straight chain alkyls. The most preferred active is where R'' is n-octyl.

The key feature of the active according to Formula 1 is that it comprises a metal salt of one of the OH groups represented by R. Where this metal has a valency of more than 1 as many of the molecules of Formula 1 as is required to function as a counter ion will exist.

Preferably the metal is an alkali metal selected from Group Ia of the Periodic Table or an alkaline earth metal selected from Group IIa. However, the salt counterion may also be an ammonium group.

Wherein the metal is an alkali metal at least one R will be selected from the group consisting of: -OK, -ONa, and, -OLi, preferably -ONa.

According to Formula 1 z is from 1 to 5 and is preferably 1 or 2, more preferably 1.

According to Formula 1 R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl.

Manufacture of such compounds as represented by Formula 1 would be a simple step for the man skilled in the art to carry out.

The most preferred antimicrobial agent is the sodium salt of n-octyl parahydroxy benzoate because it has the greatest antimicrobial effect against the commonly present oral microflora.

The compound according to Formula 1 is preferably present in an amount such that an antibacterial effect can be provided. In practice this ranges from 0.15 to 30% by weight of the composition according to the invention. Preferably, in an amount ranging from 0.2 to 10% by weight and even more preferably from 0.1 to 3.5% by weight.

The composition according to the invention may also comprise a divalent metal salt. Preferably, the divalent metal salt is a salt selected from the group consisting of zinc- and stannous salts such as zinc citrate, zinc sulphate, zinc glycinate, sodium zinc citrate, stannous pyrophosphate and

mixtures thereof. The preferable divalent metal salt is zinc citrate.

Suitably, the amount of divalent metal salt ranges from 0.01 to 10% by weight of the composition, preferably from 0.05 to 5% by weight, more preferably from 0.1 to 2% by weight and especially preferably from 0.3 to 0.9% by weight of the composition.

The oral composition according to the invention comprise further ingredients which are common in the art, such as:

antimicrobial agents, e.g. Triclosan, chlorhexidine, sanguinarine extract, metronidazole, quaternary ammonium compounds, such as cetylpyridinium chloride; bis-guanides, such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; and halogenated bisphenolic compounds, such as 2,2' methylenebis-(4-chloro-6-bromophenol);

anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin etc.;

anti-caries agents such as sodium- and stannous fluoride, aminefluorides, sodium monofluorophosphate, sodium trimeta phosphate and casein;

plaque buffers such as urea, calcium lactate, calcium glycerophosphate and strontium polyacrylates;

vitamins such as Vitamins A, C and E;

plant extracts;

desensitising agents, e.g. potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, potassium nitrate and strontium salts;

anti-calculus agents, e.g. alkali-metal pyrophosphates, hypophosphite-containing polymers, organic phosphonates and phosphocitrates etc.;

biomolecules, e.g. bacteriocins, antibodies, enzymes, etc.;

flavours, e.g. peppermint and spearmint oils;

proteinaceous materials such as collagen;

preservatives;

opacifying agents;

colouring agents;

pH-adjusting agents;

sweetening agents;

pharmaceutically acceptable carriers, e.g. starch, sucrose, water or water/alcohol systems etc.;

surfactants, such as anionic, nonionic, cationic and zwitterionic or amphoteric surfactants;

particulate abrasive materials such as silicas, aluminas, calcium carbonates, dicalciumphosphates, calcium pyrophosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, including agglomerated particulate abrasive materials, usually in amounts between 3 and 60% by weight of the oral care composition.

humectants such as glycerol, sorbitol, propyleneglycol, xylitol, lactitol etc.;

binders and thickeners such as sodium carboxymethyl-cellulose, xanthan gum, gum arabic etc. as well as synthetic polymers such as polyacrylates and carboxyvinyl polymers such as Carbopol®;

polymeric compounds which can enhance the delivery of active ingredients such as antimicrobial agents can also be included;

buffers and salts to buffer the pH and ionic strength of the oral care composition; and

other optional ingredients that may be included are e.g. bleaching agents such as peroxy compounds e.g. potassium peroxydiphosphate, effervescing systems such as sodium bicarbonate/citric acid systems, colour change systems, and so on.

Liposomes may also be used to improve delivery or stability of active ingredients.

The oral compositions may be in any form common in the art, e.g. toothpaste, gel, mousse, aerosol, gum, lozenge, powder, cream, etc. and may also be formulated into systems for use in dual-compartment type dispensers.

Embodiments according to the invention shall now be discussed with reference to the following non-limiting examples.

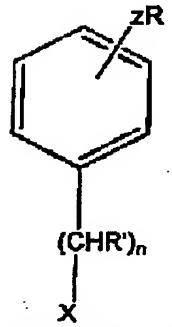
EXAMPLE

The following is a formulation according to the present invention. It is made by known processes.

Ingredient	%w/w
70% aq.sorbitol	45.0
Saccharin	0.2
Polyethylene glycol	2.0
Titanium dioxide	1.0
Sodium fluoride	0.32
Thickening silica	9.0
Abrasive silica	10.0
SLS	1.6
Sodium carboxymethylcellulose	0.8
Flavour	1.0
Zinc citrate trihydrate	0.75
Sodium salt n-Octyl paraben	1.0
Water	to 100

CLAIMS

1. An oral composition comprising a compound of Formula 1:



Formula (1),

wherein:

at least one R is an alkali metal or ammonium salt of -OH, the remaining R groups independently selected from the group consisting of: H, F, Cl, Br, -OH, Cl to C_5-alkyl, -C(O)H, and -C(O)-Cl to C_5-alkyl and z takes a value of from 1 to 5;

R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', and $-SO_2$-R''; and R'' is selected from the group consisting of: $-C_{9-16}$ alkyl or $-CH_2C_6H_6$.

2. An oral composition according to claim 1, wherein X is-C(O)O-R''.

3. An oral composition according to claim 1 or 2, wherein R'' is an aliphatic alkyl group.

4. An oral composition according to any preceding claim, wherein R'' represents a straight chain alkyl group comprising from 5 to 12 carbon atoms.

5. An oral composition according to any preceding claim, wherein the alkali metal is selected from Group Ia of the Periodic Table.

6. An oral composition according to claim 5, wherein at least one R is selected from the group consisting of: -OK, -ONa, and, -OLi.

7. An oral composition according to claim 6, wherein at least one R is -ONa.

8. An oral composition according to one of claims 1 to 4, wherein the alkali metal is selected from Group IIa of the Periodic Table.

9. An oral composition according to any preceding claim, wherein -R'' is C_6-C_{12}-alkyl.

10. An oral composition according claim 9, wherein -R'' is C_8-alkyl.

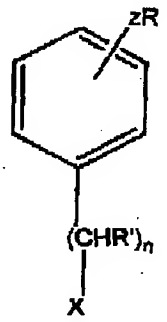
11. An oral composition according to any preceding claim, wherein z is 1.

12. An oral composition according to any preceding claim, wherein the compound of formula I is present in the composition in the range of from 0.001 to 5% by weight.

13. Oral composition according to any preceding claim wherein the composition comprises an agent selected from the group consisting of anti-caries agents, anti-tartar agents, anti-oral malodour agents, tooth whitening agents, breath freshening agents and mixtures thereof.

ABSTRACT

An oral composition comprising a compound of Formula 1:



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R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer of from 0 to 12;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', and $-SO_2$-R''; and R'' is selected from the group consisting of: $-C_5$-$_{16}$ alkyl or $-CH_2C_6H_6$.